

Listing of Claims:

This listing of the claims will replace all prior versions and listings of claims in the application:

Claims 1-29 (cancelled)

Claim 30 (previously presented): Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a target for the identification of agents which modulate DNA replication.

Claim 31 (previously presented): Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a target for the inhibition of cell proliferation.

Claim 32 (previously presented): A screening method for the identification of agents which modulate DNA replication wherein the screening method comprises the use of Ciz1 nucleotide or polypeptide sequence or any fragment or variant thereof.

Claim 33 (currently amended): The screening method according to claim 32 wherein said method comprises detecting or measuring the effect of an agent on a nucleic acid molecule selected from the ~~groups~~ group consisting of:

- a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of ~~Figures 14, 15 or 21~~ SEQ ID NO: 45, 46, 66, 67, 68, 69, 70, 71, 72 or 73;
- b) a nucleic acid molecule which hybridises to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;
- c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to ~~the sequences~~ a sequence in a) and or b) ~~and a candidate agent to be tested;~~
- d) a nucleic acid molecule which has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence in (a) and which has Ciz1 activity; and
- e) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence.

Claim 34 (previously presented): The method according to claim 33 wherein said nucleic acid molecule is modified by deletion, substitution or addition of at least one nucleic acid residue of the nucleic acid sequence.

Claim 35 (currently amended): The screening method according to claim 32, wherein said method comprises one or more of the following steps:

(i) forming a preparation comprising a candidate agent to be tested and a polypeptide molecule, or an active fragment thereof, encoded by a nucleic acid molecule selected from the group consisting of:

a) a nucleic acid molecule comprising a nucleic acid sequence represented in any of Figures 14, 15, or 21 SEQ ID NO: 45, 46, 66, 67, 68, 69, 70, 71, 72 or 73;

b) a nucleic acid molecule which hybridizes to the nucleic acid sequence in (a) and which has Ciz1 activity or activity of a variant thereof;

c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) ~~and a candidate agent to be tested;~~

d) a nucleic acid molecule which has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence in (a) and which has Ciz1 activity; and

e) a nucleic acid molecule derived from the genomic sequence at the Ciz1 locus or a nucleic acid molecule that hybridises to the genomic sequence; and

(ii) detecting or measuring the effect of the agent on the activity of said polypeptide.

Claim 36 (previously presented): The method according to claim 35 wherein said polypeptide is modified by deletion, substitution or addition of at least one amino acid residue of the polypeptide sequence.

Claim 37 (previously presented): The method according to claim 32 wherein said screening method is a cell-based screening method.

Claim 38 (previously presented): The method according to claim 37 wherein the cell naturally expresses the Ciz1 polypeptide.

Claim 39 (previously presented): The method according to claim 37 wherein the cell is transfected with a nucleic acid molecule encoding Ciz 1 or a fragment or variant thereof.

Claim 40 (currently amended): An agent ~~selected from the group consisting of: polypeptide or nucleic acid probe; polypeptide; peptide; aptamer; chemical; antibody; nucleic acid~~ which binds to the Ciz1 nucleotide or polypeptide sequence, or any fragment or variant thereof and which modulates DNA replication, wherein the agent is selected from the group consisting of: polypeptide or nucleic acid probes; polypeptides; peptides; aptamers; chemicals; antibodies; and nucleic acid molecules.

Claim 41 (currently amended): An agent according to claim 40 wherein said agent is an antibody ~~molecule~~ and binds to any of the sequences represented by ~~Figure 16, 17, or 20~~ SEQ ID NO: 26, 47, 58, 59, 60, 61, 62, 63, 64 or 65.

Claim 42 (currently amended): An antibody ~~molecule~~ according to claim 41 wherein said antibody is a monoclonal antibody.

Claim 43 (previously presented): An agent according to claim 40 wherein said agent is an anti-sense nucleic acid molecule or RNAi which binds to and thereby blocks or inactivates the mRNA sequence of Ciz1 or any fragment or variant thereof.

Claim 44 (currently amended): An agent according to claim 43 wherein said agent binds to any part of the sequences illustrated in ~~Figures 14, 15, or 21~~ SEQ ID NO: 45, 46, 66, 67, 68, 69, 70, 71, 72 or 73 or in part (i) b-d of claim 32.

Claim 45 (previously presented): An agent according to claim 43 wherein said agent binds to mRNA sequences created at alternatively spliced sites.

Claim 46 (previously presented): An agent according to claim 45 wherein said agent binds to the mRNA sequence created by alternative splicing at exon 14 of Ciz 1.

Claim 47 (previously presented): An agent according to claim 45 wherein said agent binds to the mRNA sequence created by exon skipping of exon 4 of Ciz 1.

Claim 48 (currently amended): A vector for delivering an antisense or RNAi molecule to a cell wherein the vector includes an expression cassette comprising ~~the~~ a nucleotide sequence selected from the group consisting of:

- a) the nucleic acid sequence which encodes Ciz1 amino acid sequence as shown in Figs 14, 15, ~~and 21~~ SEQ ID NO: 45, 46, 66, 67, 68, 69, 70, 71, 72 or 73;
- b) a nucleic acid molecule which hybridizes to the nucleic acid sequence of (a);
- c) a nucleic acid molecule which has a nucleic acid sequence which is degenerate because of the genetic code to the sequences in a) and b) and any sequence which is complimentary to any of the above sequences;
- d) a nucleic acid molecule which has a nucleic acid sequence that is at least 95% identical to the nucleic acid sequence in (a) and which has Ciz1 activity; and
- e) a nucleic acid sequence that encodes Ciz1 pre-mRNA (i.e., the genomic sequence).

Claim 49 (previously presented): A vector according to claim 48 wherein the expression cassette is transcriptionally linked to a promoter sequence.

Claim 50 (currently amended): Use of a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof as a diagnostic, prognostic or therapeutic reagent.

Claim 51 (previously presented): A diagnostic method for the identification of proliferative disorders comprising detecting the presence or expression of the Ciz 1 gene, Ciz1 splice variants and mutations in the genomic or protein sequence thereof.

Claim 52 (currently amended): A diagnostic method according to claim 51 wherein said method comprises one ~~of~~ or more of the following steps:

- (i) contacting a sample isolated from a subject to be tested with an agent which specifically binds a polypeptide with Ciz 1 activity or a nucleic acid molecule encoding a polypeptide with Ciz 1 activity; and
- (ii) detecting or measuring the binding of the agent on said polypeptide or nucleic acid in said sample;
- (iii) measuring expression levels of Ciz1 and Ciz1 isoform using use of reverse-transcribed PCR or real-time PCR ~~to monitor Ciz1 and Ciz1 isoform expression and to measure expression levels;~~
- (iv) measuring the presence of nucleic acid or amino-acid mutations based on altered conformational properties of the molecule; and
- (v) sequence determination, ~~optionally comprising an array based sequencing chip.~~

Claim 53 (previously presented): A pharmaceutical comprising an agent according to claim 40 in association with a pharmaceutically acceptable carrier, excipient or diluent.

Claim 54 (previously presented): A pharmaceutical comprising a Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof which binds to Ciz 1 alternate splice variants, in association with a pharmaceutically acceptable carrier, excipient or diluent.

Claims 55 and 56 (cancelled)

Claim 57 (currently amended): A method for the treatment of a proliferative disease in an animal, comprising administering to the animal ~~Use of an agent according to claim 40 for the manufacture of a medicament for the treatment of proliferative disease.~~

Claim 58 (currently amended): A method for the treatment of a proliferative disease in an animal, comprising administering to the animal a ~~Use of Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof for the manufacture of a medicament for the treatment of proliferative disease.~~

Claim 59 (currently amended): The method Use according to claim 57 or claim 58 wherein said proliferative disease is cancer.

Claim 60 (currently amended): The method Use according to claim 59 wherein said cancer is a paediatric cancer ~~and is~~ selected from the group consisting of: retinoblastoma, neuroblastoma, Burkitt lymphoma, medulloblastoma, and Ewings Sarcoma family tumours (ESFTs),

Claim 61 (currently amended): The method Use according to claim 59 wherein said cancer is a carcinoma, adenocarcinoma, lymphoma or leukemia.

Claim 62 (currently amended): The method Use according to claim 57 or 58 wherein said disease is liver, lung or skin cancer or metastasis.

Claim 63 (cancelled).

Claim 64 (previously presented): A kit comprising an agent according to claim 40.

Claim 65 (previously presented): A kit comprising Ciz 1 nucleotide or polypeptide sequence, or any fragment or variant thereof which binds to Ciz 1 alternate splice variants.